

REMARKS/ARGUMENTS

Claims status

Claims 1-79 are pending in this application. Claims 14, 15, 19, 78 and 79 are withdrawn from consideration as being drawn to a nonelected Group or Species. The claims currently under consideration are 1-13, 16-18, and 20-77.

The invention

The present invention provides methods, apparatus and computer program code for determining the genotype of one or more individuals. The methods of the invention use at least one measure of the amount of an allele of one or more genetic markers; this measure of the amount of an allele is used in statistical methods described in the present application to determine the genotype of the one or more individuals.

35 U.S.C. §101 rejection

Claims 1-13, 16-18, and 20-77 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. Applicants respectfully traverse this rejection. Applicants respectfully submit that the process of identifying the genotype of one or more individuals clearly provides a useful, concrete and tangible result. In particular, the process of identifying the genotype of one or more individuals is of particular applicability in the field of molecular biology, as well as all of its research and industrial applications. Identification of the genotype is itself a tangible result, because it represents aspects of the genetic code of the individual, which is not an abstract idea but a tangible physical quality. Furthermore, the instant invention is a method of genotyping, such as those used to determine HER2/neu status of breast cancer patients, or the genotype of cystic fibrosis or sickle cell anemia. This is not “a genetic algorithm” as characterized by the Examiner on page 3 of the Office Action, but is rather a method for ascertaining an individual genotype.

The statistical techniques used in the instant invention are utilized to identify the genotypes in the DNA samples. The method of determining a genotype of at least one

individual, as is described in the present application, fulfills the requirements of §101 by providing a useful, concrete and tangible result which is specific, substantial and credible, and Applicants respectfully request this rejection be withdrawn.

35 U.S.C. §112 rejection

Claims 21, 24 and 68 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that is regarded as the invention.

Examiner points to the limitation “the distance based clustering process yields a minimum maximum standard deviation for a distribution...” and states that the metes and bounds of the phrase “minimum maximum” are not clearly described.

Applicants respectfully traverse this rejection and suggest that Examiner has mischaracterized this claim limitation. The complete phrase is not “minimum maximum” but is rather “minimum maximum standard deviation”, i.e., the lowest value for the “maximum standard deviation” obtained by the distance-based clustering process. The methods by which the “maximum standard deviation” and the minimum of that maximum standard deviation are calculated are fully described in the specification, for example in paragraphs [0091] through [0094]. The value of the minimum maximum standard deviation is used in the methods of the instant invention to process genetic information. For example, in an embodiment described in paragraph [0094], a maximum standard deviation for each subset of data is compared with the maximum standard deviation obtained for the prior subset in a pair-wise comparison to provide: “the minimum maximum standard deviation. If the subsequent maximum standard deviation is less than the current maximum standard deviation, the former value is rejected in favor of the subsequent value 419.” Thus, the specification fully supports claims 21, 24 and 68 and meets the requirements under 35 U.S.C. §112, and Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. §103 rejections

Anderson et al. in view of Geever et al.

Claims 1-3, 5-7, 63 and 73 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al.

Anderson et al. describes the use of two-dimensional protein maps to differentiate cell types, using multivariate statistics to analyze the patterns of protein expression in each cell line to determine if the cell lines can be sorted into groups of different cell types. The data in Anderson et al. are generated from two-dimensional gels of protein samples. The gels are analyzed using a densitometer. Those data are then subjected to cluster analysis to identify patterns of protein expression, which are then used differentiate among cell lines.

Anderson et al. teaches the measuring of “abundances of numerous proteins”, but fails to teach the “method for determining a genotype” of the claimed invention. As the Examiner will appreciate, the measure of protein levels is not equivalent to the measure of the amount of an allele (e.g., SNPs). Anderson et al. also fails to teach “a method for determining a genotype of at least one individual” by “using at least one measure of the amount of a given allele” as described in the instant application; in fact, as the Examiner has pointed out, Anderson et al. completely fails to “explicitly mention the term genotype”. *see* Office Action, page 7.

Geever et al. teaches the analysis of a specific single nucleotide polymorphism in human hemoglobin genes, which is associated with sickle cell anemia. Depending on the identity of the allele at this nucleotide position, digestion of the DNA molecules (using a specific endonuclease – *DdeI*) containing this nucleotide sequence will differ. The method described in Geever et al. uses a particular restriction enzyme analysis at a single nucleotide position to determine the genotype of an individual for only that nucleotide position. If an individual has normal hemoglobin, digestion with the restriction endonuclease *DdeI* results in two bands of 175 bp and 201 bp length. If an individual is heterozygous at this site, digestion results in an extra band at 376 bp. If an individual is homozygous for the sickle cell mutation, the band at 376 bp is present, but the band at 175 bp is lost.

The methods of Geever et al. are thus limited to only one particular nucleotide position, because the fortuitous change in the restriction site for the *DdeI* enzyme depends on the allele in that nucleotide position and does not translate to other positions of the genome. Thus, for example, regarding Table I of Geever et al., the described method of SNP detection will only work if the allele changes from CTGAG to CTGTG (or vice versa). As the Examiner will appreciate, this specific test for this specific SNP is not translatable to other SNPs with different sequences, and Geever et al. therefore fails to teach the methods of the present invention.

To construct a *prima facie* case of obviousness, the cited references must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991). Applicants respectfully submit that each of the required criteria set forth above have not been satisfied, and thus, a *prima facie* case of obviousness has not been established. Applicants' respectfully traverse the §103 rejections for the reasons set forth below.

(1) There is no motivation to combine the cited references

There is no motivation to combine Anderson et al. and Geever et al., because the two references involve different kinds of data. Anderson et al. uses data from two-dimensional protein maps, whereas Geever et al. uses restriction endonuclease analysis of DNA. A person of skill in the art would not be motivated to take the DNA gel data from Geever et al. to use in the statistical methods of Anderson et al., and there is nothing in either reference that suggests a motivation for such a combination.

Furthermore, the data from Geever et al. can not be translated to be used in the methods of Anderson et al., because Anderson et al. describes methods for generating statistical data sets, in which each sample is "looked upon as a point in a 285-dimensional space", in which the gel patterns correspond to a distribution of 16 points. *see* Anderson et al., page 2033, last paragraph,

right column. Data regarding the allele at a single nucleotide position as described in Geever et al. can not be used in the analyses described in Anderson et al., because the single data point from Geever et al. would remove the need for the probability clustering methods of Anderson et al. Thus, the proposed combination would render the statistical techniques of Anderson et al. unsuitable for their intended purpose, which means that there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

The proposed combination of references would also change the principle of operation of the prior art invention being modified, again because the single point of data resulting from Geever et al. would obviate the need for the statistical analyses presented in Anderson et al. As the Examiner will appreciate, this would mean that the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810 (CCPA 1959).

(2) There would be no expectation of success from combining the cited references

One of skill in the art would have no expectation of success in performing the instant invention upon combining Anderson et al. and Geever et al., because Geever et al. provides a “yes or no” response regarding the identity of an allele at a specific nucleotide position, while Anderson et al. uses multivariate statistical analysis of data from two-dimensional protein gels to differentiate between cell lines. One of skill in the art would not expect to successfully determine “a genotype of at least one individual from a genetic marker using at least one measure of the amount of a given allele” by combining the restriction endonuclease analysis of Geever et al. with the methods of Anderson et al. The two references do not teach methods which use the same type of data, nor are the data from either reference easily translated for use with the other.

The Examiner states that it would have been obvious to someone of ordinary skill in the art to have a reasonable expectation of success in practicing the claimed invention upon combining the references because “while Anderson teaches a general probabilistic clustering method to analyze expression of genes Geever teaches the advantages of genotyping SNPs in humans.” *see* Office Action, page 8. However, as discussed above, Applicants respectfully submit that the method of Anderson et al. does not correspond to the genotyping method of the

instant invention, because although there is some correlation between gene expression and protein levels, a quantification of protein abundance does not provide a quantification of the level of a particular allele. In addition, the claims of the instant invention are not limited to only the genotyping of SNPs, but instead provide methods for using “at least one measure of the amount of a given allele” of a genetic marker. In contrast, Geever et al. is limited to analysis of only a single SNP, and one of skill in the art would have no reasonable expectation of success upon combining Geever et al. with Anderson et al.

(3) The references fail to describe every element of the claimed invention

When combined, Anderson et al. and Geever et al. fail to describe every element of the claimed invention. Anderson et al. uses data from two-dimensional radiograms of gels which reflect the presence of certain proteins – as quoted by the Examiner: “In this paper we discuss methods for generating statistical data sets in which the abundances of numerous proteins are measured across samples (gels).” *see* Office Action pages 6-7. Anderson et al. thus fails to teach the use of “at least one measure of the amount of a given allele” of the claimed invention; Anderson et al. also fails to teach “assigning the measure of the amount of the allele to a group” and “assigning a genotype to the group” as is described in the instant application. The quantification of protein expression in Anderson et al. does not correlate to the quantification of the amount of a given allele in the claimed invention.

Geever et al. fails to rectify the deficiencies of Anderson et al., because Geever et al. only describes one particular SNP related to sickle cell anemia. The data from Geever et al. can not be generalized to the methods of the claimed invention, because Geever et al. is limited to the fortuitous result of a single restriction site which is altered based on the identity of the allele at a single nucleotide position. Thus, the combination of the cited references does not describe every element of the claimed invention, because the combination of the references fails to provide methods “for determining a genotype of at least one individual” by “using at least one measure of the amount of a given allele”.

Since none of the requirements for a *prima facie* case of obviousness under 35 U.S.C. §103(a) is fulfilled by a combination of Anderson and Geever, Applicants respectfully request this rejection be withdrawn.

Anderson et al. in view of Geever et al. and further in view of Xue et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Xue et al. does not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. and further in view of Krishna et al.

Claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. as applied to claims 1-3, 5-7, 63, and 73 and further in view of Krishna et al.

As discussed above, Anderson and Geever cannot be combined to provide the instant invention. Krishna et al. does not rectify the deficiencies of Anderson and Geever, and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. and further in view of Excoffier et al.

Claims 58-62, 63, 67 and 69-72 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. in view of Krishna et al. as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Excoffier et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Excoffier et al. does not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. in view of Krishna et al. and further in view of Montoya- Delgado et al. in view of Frey et al.

Claims 1, 25-53, 63, 65, 73 and 77 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. in view of Krishna et al. as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Montoya-Delgado et al. in view of Frey et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Krishna et al. in view of Montoya-Delgado et al. in view of Frey et al. do not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. in view of Krishna et al. and further in view of Excoffier et al.

Claims 58-62, 63, 67 and 69-72 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. in view of Krishna et al. as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Excoffier et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Krishna et al. in view of Excoffier et al. do not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. in view of Krishna et al. and further in view of Babu et al.

Claims 63 and 66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. in view of Krishna et al. as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Babu et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Krishna et al. in view of Babu et al. do not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

Anderson et al. in view of Geever et al. in view of Krishna et al. in view of Montoya-Delgado et al in view of Frey et al and further in view of Babu et al.

Claims 1, 26, 38-39, 44 and 54-57 are rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson et al. in view of Geever et al. in view of Krishna et al. in view of Montoya-Delgado et al in view of Frey et al as applied to claims 1, 25-53, 63, 65, 73 and 77 and further in view of Babu et al.

As discussed above, Anderson et al. and Geever et al. cannot be combined to provide the instant invention. Krishna et al. in view of Frey et al. in view of Babu et al. does not rectify the deficiencies of Anderson et al. and Geever et al., and thus there is no *prima facie* case of obviousness upon combination of these references. Applicants therefore respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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Reply to Office Action of 10/26/06

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,

Date: January 26, 2007

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